UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,534	11/24/2003	Jack D. Burton	330651	3647

35657 7590 08/15/2007

FAEGRE & BENSON LLP
PATENT DOCKETING
2200 WELLS FARGO CENTER
90 SOUTH SEVENTH STREET
MINNEAPOLIS, MN 55402-3901

EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

MAIL DATE	DELIVERY MODE
08/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,534	BURTON ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,11,20 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,11,20 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

1. The amendment filed June 5, 2007, is acknowledged and has been entered. Claims 4-5, 7-10, 12-19, 21-36 and 38 have been cancelled. Claim 1 has been amended.

2. Claims 1-3, 6, 11, 20 and 37 are pending in the application and are under examination.

3. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment and/or arguments filed June 5, 2007, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 27, 2007.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 102/103

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. The rejection of claims 1-3 and 20 under 35 U.S.C. 102(a), as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Willson et al (of record), is maintained.

At page 4 of the amendment filed June 5, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been fully and carefully considered but not found persuasive for the following reasons:

Applicant has argued, starting at page 5, last paragraph, of the amendment filed June 5, 2007, that Willson et al provides the "mere suggestion that a chimeric molecule might include NR4 and an immunoglobulin. This is merely one suggestion from a list of

possible suggestions, including NR4 and a haemopietin receptor [sic], NR4 and a receptor tyrosine kinase, NR4 and TNF/NGF receptors, NR4 and G protein-coupled receptors, NR4 and toxins and NR4 and growth factors. No actual working example, showing a fusion of NR4 with any cell-targeting antibody or fragment, is disclosed in Willson."

Furthermore, at page 6, 2nd paragraph, Applicant has argued "that the reference of Willson is a classic 'obvious to try' rejection, with no actual disclosure of any species within the claimed subject matter and little or no guidance provided to the skilled artisan on how to make and use an NR4-immunoglobulin fusion protein. Only the first recited passage of Willson even mentions the possibility of an immunoglobulin comprising fusion protein (among 6 other possibilities). The second cited passage concerns the incorporation of an IL-4Ra derived sequence in NR4, and the third cited passage merely states that (unspecified) fusion proteins and chimeric molecules are contemplated.

Finally, Applicant has respectfully submitted, "Willson does not provide an enabling disclosure of IL-4Rα attached to a cell-targeting antigen-binding antibody or antibody fragment, as required to support a prior art rejection under MPEP §2121.01."

In response, Applicant acknowledges that Willson teaches fusion proteins comprising NR4 polypeptides and an immunoglobulin at page 7, lines 15-21, as one example of a chimeric or fusion protein, and that Willson teaches, at page 10, lines 6-21, that the ligand-binding region of the IL-4 receptor α chain is incorporated as an NR4 polypeptide, yet argues that the disclosure of Willson is not enabling for conjugates comprising IL-4Rα attached to a cell-targeting antigen-binding antibody or antibody fragment.

Notably, MPEP §2121.01 states the following:

> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention not novel' or anticipated' within section 102, the stated test is whether a reference contains an enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. Elan Pharm., Inc. v. **>Mayo Found. For Med. Educ. & Research<, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (At issue was whether a prior art reference enabled one of ordinary skill in the art to produce Elan's claimed transgenic mouse without undue experimentation. Without a disclosure enabling one skilled in the art to produce a transgenic mouse without undue experimentation, the reference

> would not be applicable as prior art.). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed.Cir. 1985).

Contrary to Applicant's assertions, the disclosure of the claimed invention by Willson et al would have been sufficient to have enabled the artisan to make the claimed conjugates comprising IL-4Rα attached to a cell-targeting antigen-binding antibody or antibody fragment because the methodology necessary to do so was well known, conventional, and routine at the time of the invention by Applicant.

Moreover, Willson need only provide a disclosure that would permit one of ordinary skill in the art to produce the claimed fusion protein. In this case, because Willson et al teach: (a) fusion proteins comprising NR4 polypeptides and an immunoglobulin that allows targeting of the former polypeptides to particular cells or tissues (see entire document, e.g., at page 7, lines 19-21); (b) NR4 polypeptides include the ligand-binding region of the IL-4 receptor α chain (e.g., at page 10 lines 15-17 and page 11, lines 9-13); and (c) methods for making recombinant fusion proteins comprising said NR4 polypeptides (e.g., page 10, lines 6-21, Example 12 and page 29, lines 1-30), it is submitted that one of skill in the art would have readily been capable of producing those fusion polypeptides. The genetic engineering techniques typically used to produce such chimeric fusion proteins were well known in the art.

Furthermore, to address Applicant's argument that Willson et al does not teach a species of immunoglobulin, i.e. a cell-targeting antibody within the claimed subject matter, but instead teaches a cell-targeting immunoglobulin, it is submitted that one of skill in the art would immediately acknowledge that the terms "antibody" and "immunoglobulin" are generally considered synonymous. According to the definition of immunoglobulins, which is provided at page 9, of the Office action mailed March 27, 2007, the "immunoglobulins" are "a family of globular proteins that comprise antibody molecules and molecules having patterns of molecular structure (antigenic determinants) in common with antibodies"[1].

[1] Elgert et al. Immunology: Understanding the Immune System, 1996, page 59.

Nevertheless, in further response to Applicant's argument, and as additional evidence of the interrelatedness of the terms "antibody" and "immunoglobulin", it is noted that Dorlands Medical Dictionary (available online at www.mercksource.com) defines the term "immunoglobulin" as meaning: "any of the structurally related glycoproteins that function as antibodies" (Copyright © 2002-2007 Merck & Co., Inc., Whitehouse Station, NJ, USA; see exhibit A).

Given these definitions, one of skill in the art would recognize that the cell-targeting "immunoglobulins" to which Willson et al. refers are antibodies or functionally equivalent molecules having structures that are very similar to antibodies.

Therefore, because the artisan would have been sufficiently enabled to produce such conjugates, the disclosure of the claimed conjugate comprising IL-4Rα attached to a cell-targeting immunoglobulin by Willson et al. anticipates the claimed invention.

For these reasons, the Examiner disagrees with Applicant's contention that the rejection has been overcome and the rejection of claims 1-3 and 20 under 35 U.S.C. 102(a), as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Willson et al (of record), is maintained.

Claim Rejections - 35 USC § 103

9. The rejection of claims 1, 6, 11 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Willson et al (of record), in view of Hu et al (of record), Fritzberg et al (of record) and Schwarz et al (of record), as evidenced Rolling et al (of record), is maintained.

At page 7 of the amendment filed June 5, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been fully and carefully considered but not found persuasive for the following reasons:

Applicant has argued that, whereas Willson fails to provide any enabling disclosure relevant to a fusion protein comprising an antigen-binding antibody or fragment attached to IL-4Rα, the deficiency is not made up for in any of the other cited references. Additionally, Applicant has argued that, according to the preceding Office

action, Hu and Fritzberg disclose attachment of targeting antibodies to IL-2 or IL-4, but not to IL-4Rα; so, if anything, Hu et al., Fritzberg et al. and Schwarz et al. teach away from the claimed subject matter by leading the skilled artisan to believe that antibodies or fragments should be attached directly to interleukins, as opposed to an interleukin receptor protein.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, contrary to Applicant's assertions, the combination of these references does not teach away from targeting moieties comprising a conjugate of an antibody specific for HLA-DR linked to the ligand-binding region of interleukin-4 receptor α (IL-4R α) as these references provide the motivation for one of skill in the art to make the claimed invention with a reasonable expectation of success. Notably, at page 7, 3rd paragraph, the Applicant has mischaracterized Fritzberg et al. suggesting that the disclosure would lead the skilled artisan to directly attach IL-4, and not the interleukin-4 receptor α (IL-4Rα) to a targeting antibody. However, contrary to Applicant's assertions, as set forth at page 11 of the Office action mailed March 27, 2007, Fritzberg et al., teaches directly linking one member of a ligand/anti-ligand pair for pre-targeting tumors with anti-tumor active agents such as IL-4. Therefore, Fritzberg et al. does not teach directly conjugating IL-4 to the cell-targeting antibody, as the cell-targeting antibody is used to pre-target the tumor, so that when active tumor agents, such as IL-4 are administered there will be improved targeting of the tumor by the active agent and less exposure of non-target tissues with the active agent. (see e.g., columns 1, 3 and 4).

Therefore as explained in the previous Office action, based on the combination of these references, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a targeting moiety comprising a conjugate of an antibody specific for HLA-DR linked to the ligand-binding region of interleukin-4 receptor α (IL-4Rα). Notably, as Willson et al teach fusion proteins

comprising interleukin-4 receptor α, which is the ligand-binding region of IL-4, Hu et al teach that lymphoma cells express an antigen targeted by the Lym-1 antibody and a fusion protein targeting moiety comprising the Lym-1 [i.e., anti-HLA-DR] and IL-2 which is cytotoxic to lymphoma cells and Schwarz et al teach that IL-4 is cytotoxic to lymphoma cells, it would have been obvious to one of ordinary skill in the art to make a targeting moiety comprising a conjugate of an antibody specific for HLA-DR linked to the ligand-binding region of interleukin-4 receptor α (IL-4R α) to, for example, pre-target lymphoma cells with a conjugate that would bind to the lymphoma cells as well as target IL-4 to directly to the tumor cells, to improve targeting of IL-4 to the lymphoma cells and reduce exposure of non-target tissue to IL-4. Therefore, as Fritzberg et al teach the advantages of pre-targeting target cells and Hu et al and Schwarz et al teach the advantages of targeting lymphoma cells with HLA-DR antibodies and IL-4, respectively, one of ordinary skill in the art would have been motivated to make a targeting moiety comprising a conjugate of an antibody specific for HLA-DR linked to the ligand-binding region of interleukin-4 receptor α (IL-4Rα). Furthermore, as Hu et al teach that fusion proteins comprising HLA-DR antibodies target lymphoma cells successfully, one of ordinary skill in the art would have a reasonable expectation of success in making such conjugates. Finally, as evidenced by Rolling et al at page 10 of the Office action mailed March 27, 2007, the IL4Rα subunit is the same as the IL13Rα subunit.

For these reasons, the Examiner disagrees with Applicant's contention that the burden of showing a *prima facie* case of obviousness was not met by the first Office action on the merits; and since Applicant has provided no compelling arguments that the cited references would not have rendered the claimed subject matter obvious to one of ordinary skill in the art at the time the invention was made, the rejection of claims 1, 6, 11 and 37 is maintained.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. The rejection of claims 1-3 and 20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of US Patent No. 6,703,488 as evidenced by Rolling et al (FEBS Letters 393:53-56, 1996), is maintained for the reasons of record, as explained in the previous Office action.

At page 7, last paragraph, of the amendment filed June 5, 2007, Applicant has indicated that a terminal disclaimer will be submitted when allowable subject matter has been found in the instant application.

Accordingly, this rejection will be maintained until it is appropriately resolved.

New Ground of Rejection

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-3, 6, 11 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

Claim 1 has been amended to recite that said antibody comprises any of a plurality of "antigen-binding variable region domains", where it is unclear how this term is to be understood.

Applicant has indicated that support for this amendment can be found "in the published Specification (Publ. No. 20040077843) at least at Paragraph [0022], which recites that, 'Suitable antibody fragments include F(ab')2, F(ab)2, Fab', Fab, Fv and the like, including hybrid fragments. Also useful are any subfragments that retain the hypervariable, antigen-binding region of an immunoglobulin'."

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support for the language of the claims, particularly since the meaning of the term "antigen-binding variable region domain", as now recited in the claims, cannot be determined.

Notably, paragraph [0022] of the published application (Publ. No. 20040077843) discloses subfragments that retain **the** hypervariable, antigen-binding region of an immunoglobulin. In fact, subfragments of antibodies, such as F(ab')2, F(ab)2, Fab', Fab, and Fv, comprise either one or two antigen-binding regions; but it is not apparent that the "antigen-binding variable region domains" to which the claims are now directed

are not necessarily equivalent, nor limited to **the** hypervariable, antigen-binding regions of an immunoglobulin that are comprised by any of such subfragments. Moreover, the specification does not describe what is to be considered a "domain" or "domains" of the "antigen-binding variable region".

Accordingly, the scope of the instant claims includes antibodies that comprise any of a plurality of "domains" of either of the "antigen-binding variable regions" of an antibody, where the "domains" might be said to be *specific* for a cell marker, yet where the antibody does not necessarily have the ability to bind specifically bind to the cell marker. For example, the antibody to which the claims are directed might comprise the variable region of a heavy or light chain polypeptide of an antibody, either of which may be described as *specific* for a cell marker; yet such an antibody comprising just such a "domain" would not necessarily bind to the cell marker because it comprises only a portion of the antigen binding domain of the antibody.

Given the apparent difference in the breadth of the claims and that of the pertinent disclosures, it is submitted that the amendment has introduced new concepts, violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Paragraph [0022] of the published application would at best only support a claim directed to antibody fragments comprising one (e.g., Fab) or two (e.g., F(ab')2) of the hypervariable, antigen-binding regions of an immunoglobulin. Therefore, it is suggested that it would be remedial to amend claim 1 to recite, for example, "said antibody comprising the antigen-binding variable region of an antibody that specifically binds a cell marker specific to a targeted cell".

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

bd
August 13, 2007

immunoglobulin (im·mu·no·glob·u·lin) (im"u-no-glob'u-lin) any of the structurally relatec glycoproteins that function as antibodies, divided into five classes (IgM, IgG, IgA, IgD, and IgE) on the basi of structure and biologic activity. The basic structural unit of the immunoglobulin molecule, referred to as a monomer, is a Y-shaped molecule composed of two heavy (H) chains and two light (L) chains (see accompanying illustration). IgD, IgG, and IgE occur only as monomers; IgM and IgA may occur as monomers or polymers. The polymeric forms contain an additional polypeptide called the J chain, and secretory IgA contains another structure called the secretory component (SC). Each chain consists of a variable region (V_H or V_L) and a constant region (C_H or C_L), which are coded for by different genes. Parts of the V_H and V_L regions make up the antigen-binding site, one on each "arm" (Fab region) of the monomer. An individual can make about 10^4 different V_H regions and 10^3 V_L regions, which combine to make about 10^7 different antigen-binding sites, each with a distinct antigenic specificity. Parts of the C_H regions make up the "body" (Fc region) of the monomer, which contains various sites responsible for the biological activity of the molecule. In any one immunoglobulin molecule, all of the H chains are identical, as are the L chains. The C_H region determines both the heavy chain class to which the H chain belongs and the immunoglobulin class to which the molecule belongs. The H chain classes are denoted by the Greek letters (μ, δ, γ, ε, and α) corresponding to the Latin letters of the immunoglobulin classes, e.g., μ to IgM. There are two types of light chains (denoted κ and λ), either of which may combine with any of the heavy chains and thus occur in any of the immunoglobulin classes. In human immunoglobulins, three of the classes (IgM, IgG, and IgA) have subclasses; i.e., there are several similar but distinct C_H region genes in these classes. In addition, the λ light chain type has subtypes. The subclasses (subtypes) are denoted by numerical suffixes, e.g., IgG1 and γ1 subclasses and λ2 subtype. Immunoglobulins (monomeric IgM and IgD) first appear on the surface of B cells as antigen receptors. When a cell is activated by contact with antigen and differentiates into a plasma cell, the cell continues to produce the same L chain and V_H regior of the H chain, but gene rearrangement may occur to attach this V_H region to a different C_H region (class switching). Thus the secreted immunoglobulin may be of any class but has the same antigenic specificity a the antigen receptors of the parent B cell. In addition to the effects produced solely by the binding of antige by antibody, e.g., viral neutralization or the inability of some bacteria to invade mucosal surfaces when coated by antibody, certain classes of antibodies can trigger other processes when bound to antigen: IgM and IgG activate the classic complement pathway, IgA and IgG activate the alternative pathway, and IgM, IgG1, and IgG3 act as opsonins, triggering phagocytosis of the bound antigens by macrophages and neutrophils. IgE has the unique function of mediating immediate hypersensitivity (q.v.) reactions; it binds to specific receptors on basophils and mast cells and triggers the release of mediators on contact with antige IgG is the only class transferred across the placenta, providing the fetus and neonate with protection again infection. See also *immunoglobulin genes*, under *gene*, *homology region*, under *region*, and *allotype*, *idiotype*, and *isotype*.